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Highly chemoselective oxidation of 1,5-diols to δ -lactones with TEMPO/BAIB

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Abstract—The selective oxidative conversion of a variety of highly functionalized 1°,2°-1,5-diols into the corresponding δ -lactones has been effected simply and efficiently using a reagent system comprised of catalytic 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and excess bis-acetoxyiodobenzene (BAIB). © 2002 Elsevier Science Ltd. All rights reserved.

Substituted pyran and δ -lactone moieties occur in a wide array of natural products. In our recent studies towards the synthesis of pyran containing targets phorboxazole A,¹ okadaic acid² and azaspiracid,³ we have utilized nucleophilic additions to substituted lactones to access these systems. Numerous conditions have been reported to facilitate the oxidation of a 1,5-diol to the corresponding δ -lactone (Fig. 1), including TPAP,^{3,4} PCC,^{3,5} and TEMPO/co-oxidant.⁶ However, formation of the undesired ketoaldehyde from 1°,2°-diols can be a difficult side reaction to control resulting in lower conversion to the lactone.

On this basis and with our continued interest in the use of δ -lactones as valuable synthetic intermediates, we sought a chemoselective protocol capable of oxidizing a range of 1°,2°-1,5-diols to highly functionalized δ -lactones. The selective oxidation of primary alcohols to the corresponding aldehydes in the presence of secondary alcohols with catalytic TEMPO employing bis-



Figure 1. Oxidation of 1,5-diol to δ -lactone.

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acetoxyiodobenzene (BAIB) as the co-oxidant was first reported in 1997.⁷ Herein, we report the application of this reagent system to the selective oxidation of $1^{\circ},2^{\circ}-1,5$ -diols to δ -lactones.

As shown in Table 1, a variety of substituted lactones were prepared from the corresponding diols. In general, catalytic TEMPO (10–20 mol%) and 5 equiv. of BAIB at room temperature in CH_2Cl_2 were used.⁸ Monitoring of the reaction showed the initial formation of the intermediate lactol species, which then undergoes further oxidation to the lactone. Under these conditions the monosubstituted diols 1 and 2 (entries 1 and 2) were cleanly converted to 3 and 4.⁹ The oxidation of 1° allylic diol 5 and 2° allylic diol 7 both proceeded smoothly to provide lactones 6 and 9, respectively (entries 3 and 4).

The oxidation of the highly substituted substrates **8** and **11** to the corresponding lactones was readily achieved under the standard reaction conditions (entries 5 and 6). The application to the formation of fused ring system **12** was demonstrated using tetrahydrofuran-diol **11** (entry 6).

The intermediacy of a hydroxy aldehyde species resulting from selective oxidation of the primary $alcohol^{6b}$ was confirmed for substrate **8** by stopping the reaction at shorter reaction times and isolating the corresponding lactol. However, the partial oxidation was difficult to control and provided variable amounts of lactol and lactone. From **8**, a 5:1 ratio was the highest proportion of lactol:lactone that could be practically isolated.

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Table 1. Oxidation of 1,5-diols with TEMPO/BAIB

entry	substrate	product	time (h)	yield (%) ^a
1	TBDPSO,, OH OH	TBDPSO,,,000	20	94
2	1 РМВО, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	3 PMBO, , ,0,0 4	16	77
3	Bno, OH OH	Bn0,,,0,0	1.5	96
4		Br ''O O	3.5	87
5		Boc ''', OH N,,,, OH 10	3.5	95
6	творезо		4	78
7	11 , ', 'OH OH 13		3.5	85

^aThe yields refer to isolated compounds after chromatography.

In summary, the effectiveness of the TEMPO-BAIB reagent system to selectively oxidize $1^{\circ}, 2^{\circ}-1, 5$ -diols to the corresponding δ -lactones has been demonstrated. The generality and functional group compatibility of this process has been highlighted through the formation of several highly substituted systems.

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- All new compounds gave spectroscopic data in agreement with the assigned structures. A typical procedure for oxidation: To a stirred room temperature solution of triol 8 (1.9 g, 4.9 mmol) in CH₂Cl₂ (25 mL) was added sequentially bis-acetoxyiodobenzene (BAIB, 5.00 g, 15.5 mmol)

and 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 0.15 g, 1.0 mmol). After stirring at rt for 3.5 h, saturated aqueous Na₂S₂O₃ and diethyl ether (50 mL) were added. The separated organic phase was washed with saturated aqueous NaHCO₃ then H₂O. The combined aqueous washes were extracted with diethyl ether (3×25 mL) and the combined organic fractions were washed with brine, dried (NaSO₄), filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography (hexanes:ethyl acetate, 2:1→1:2, v/v) to provide lactone **10** (1.76 g, 4.6 mmol, 94%) as a colorless foam: R_f 0.45 (hexanes:ethyl acetate, 1:1, v/v); [α]²⁵_D -38.9

(c 2.65, CHCl₃); IR (neat, cm⁻¹) 3476, 2979, 2936, 2878, 1742, 1695, 1457, 1387, 1181; ¹H NMR (300 MHz, C₆D₆, 70°C) δ 5.39 (d, J=9.3 Hz, 1H), 4.4 (bs, 1H), 3.72, (m, 2H), 3.54 (d, J=1.5 Hz, 1H), 3.51 (d, J=1.2 Hz, 1H), 3.25 (s, 1H), 2.16 (m, 2H), 1.9–1.45 (m, 9H), 1.4 (s, 9H), 1.2 (d, J=5.1 Hz, 3H), 0.74 (d, J=6.3 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆, 70°C) δ 173.4, 152.3, 128.9, 94.5, 87.5, 79.8, 75.5, 69.0, 68.9, 55.5, 40.2, 39.7, 28.9, 27.9, 25.0, 15.8, 11.8, 11.5; HRMS(CI) calcd for C₂₀H₃₄NO₆[(M+H)⁺]: 384.2384; found: 384.2385.

9. The prolonged reaction times indicated for entries 1 and 2 are generally not necessary.